French Republic

PARLIAMENTARY OFFICE FOR SCIENTIFIC AND TECHNOLOGICAL ASSESSMENT

Animal experimentation in Europe : What alternatives ? What ethics ? What governance ?

Summary of the report drafted on behalf of the OPECST by Messrs. Michel Lejeune and Jean-Louis Touraine, deputies

A referral was made to the OPECST (Parliamentary Office for Scientific and Technological Assessment) by the National Assembly Bureau to carry out a study on *'the principles applying to animal experimentation and alternative methods to it'*. The study was entrusted to Messrs. Michel Lejeune and Jean-Louis Touraine, deputies, and was undertaken at a time when the 1986 directive defining the conditions for using animals for experimental and scientific purposes in the European Union is in the process of being revised.

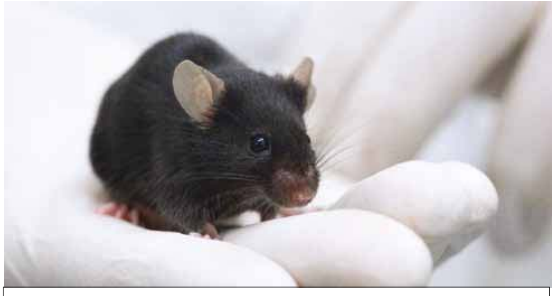
Context and issues of the study

In Europe, the principles applying to animal experimentation are defined in a 1986 directive setting forth the 3R rule devised by two British scientists in 1959: replacement of experiments on animals by alternative methods when they exist, reduction of the number of animals used, and 'refinement' aimed at limiting pain suffered by animals and ensuring their comfort.

While the 3R principles are widely recognised internationally, they are given various interpretations. Some believe that the 3Rs should apply globally, while others feel they should be implemented at the level of each protocol.

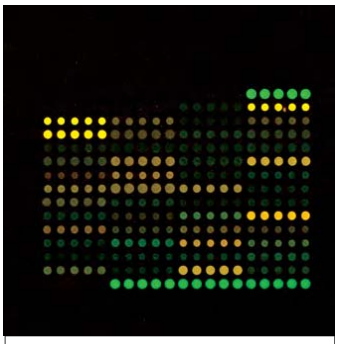
Several changes have recently taken place at the European level and nationally.

On 5 November 2008, the European Commission published a proposal to revise the 1986 directive. This revision had been announced as early as 2001 and was desired by the European Parliament. In May 2009, the latter adopted various amendments before its renewal. Negotiations are under way to reach a compromise, as the Swedish Presidency wanted to reach an agreement before the end of 2009.



Source : Home Office - Annuel report 2008

Nationally, following the *rencontres 'Animal et société'* (Animal and Society Days), organised on the initiative of the President of the Republic and as part of the Grenelle Environment Round Table process, and also with a view to the adoption of the new directive tabled under the French presidency, several initiatives have been taken: a scientific interest group for the development of alternative methods has been created and tasked with taking stock of these methods; the *comité national de réflexion éthique en expérimentation animale* (national committee deliberating on the ethics of animal experimentation), created in 2005, has published an animal experimentation charter; a collective experts' report on the pain suffered by animals has been commissioned by the public authorities; and a study has been started on education and animal experimentation.



Pain genes research
Source : Fondation Recherche 3R

The usefulness of animal experimentation is very widely recognised, both in the biomedical research field and to ensure the safety of products that are marketed. On the other hand, two strong demands have surfaced: limiting as much as possible the damage caused to animals and developing alternative methods.

The adoption of the 1986 directive represented progress, both scientifically and ethically, and its revision is awaited to reach better harmonisation, take account of the evolution of knowledge and technological progress, promote Europe's scientific attractiveness and the mobility of researchers within it, and improve the image of animal experimentation in the eye of the European public which is increasingly concerned over 'animal welfare'. Several measures proposed by the European Commission have however given rise to serious concerns within the scientific community and also the industrial world.

The level of requirements defined in Europe generates costs and is likely to extend timeframes. Also, the restrictions laid down against some forms of research are having a reducing effect on research activities and industrial activities. As standards are not harmonised internationally, there is a risk of these activities being delocalised and a balance must therefore be sought between the EU and the other regions of the world.

A balance between the various requirements of citizens must also be sought: their requirement regarding health and the safety of products, which mobilises the potential of European biomedical research and health agencies, on the one hand, and their requirement regarding animal welfare on the other hand.

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Progressive implementation is also necessary to: bring facilities into line with standards, which will improve the work conditions of researchers and personnel; develop alternative methods, which cannot be introduced by force; define breeding strategies taking account of the concerns of the public and of supply needs; and reach a better exploitation of the data from experiments on animals.

Researchers placing an anaesthetised mouse in MRI equipment. In some cases, MRI allows the number of animals used in an experiment to be reduced by 90 %.
Source : Fondation Recherche 3R

Various essential topics remain moreover barely addressed by the directive: the role of personnel, training, communication with the general public, the protection of researchers and personnel, the organisation of animal research facilities, and the search for alternative methods and their validation.

What alternatives ?

Currently some 12.1 million animals are used for scientific or experimental purposes in Europe: 77.5% are rodents and approximately 12,000 primates are used. The statistics made available to the public, for which no explanatory comments are given and which are not supported by any retrospective or prospective analyses, are scarcely harmonised in Europe. Moreover, no official statistics are available internationally.

The public authorities are being vigilant regarding the evolution of this number for several reasons. First, the use of animals for experimental purposes is costly as it requires adapted facilities and qualified personnel. Second, animal protection associations regard the evolution of the number of animals used as a criterion of the effectiveness of the public policies implemented to regulate animal experimentation.

That's why, at European level, within the framework of the various regulations adopted, and at the national level, especially in the framework of the Grenelle Environment Round Table process, the development of alternative methods is recommended. This development is all the more necessary as several indications suggest an increase in the number of animals used.

The main factors leading to this increase are: the use of transgenic models; implementation of the REACH regulation, despite the mechanisms set in place to promote data sharing and limit the number of tests; and the need to find new treatments and ensure better product safety, with new tests on endocrine disruptions or reproductive toxicity. In addition to these factors, there are also, paradoxically, the changes introduced by the initial proposal to revise the directive, which extends the scope of the regulation to some invertebrates and some larval or embryonic forms which, moreover, are often used as alternative models.

In the light of this situation, few advances have been proposed by the European Commission in its proposal for a revision. The only innovation has consisted in providing for the creation in each Member State of a reference laboratory, like that in Germany (ZEBET). The European Parliament has, for its part, preferred to broaden the role of the ECVAM (European Centre for the Validation of Alternative Methods), despite the reservations put forward against its current operation.

To date, few alternative methods have been validated. In the field of chemicals, including cosmetics, only fifteen or so methods have been validated by the OECD; they concern five types of toxicity tests: mutagenesis, skin corrosion, skin absorption, phototoxicity and skin irritation (ongoing).

Two obstacles have been identified, such as the absence of any real coordinated replacement strategy at the European level, related in part to the low involvement of States, and the unwieldiness of validation procedures internationally, which are a prerequisite for the mutual acknowledgement of tests. Referring to funding, as part of the FPRDs, 150 million euros has been assigned to the development of alternative methods over the past 20 years; in July 2009, a partnership was concluded between the Commission and the cosmetics industry (the COLIPA), for an amount of 100 million euros over 5 years, in order to develop new alternative methods, especially in the field of systemic toxicity, so as to prepare for the 2013 deadline laid down by the 'cosmetics directive' which bans the use of animals to test cosmetics marketed in Europe.

The low number of alternative methods validated today must not however hide the progress achieved as regards the optimisation of protocols, which fits into a reduction logic.

While, since 1986, the number of animals used has greatly decreased until the last few years, this is due to the generalised use of various technologies which, without replacing animals, have reduced the number of animals used in each procedure: *in vitro* technologies, imaging, high-throughput screening, and mathematical modelling. Efforts are continuing in this field, in a spontaneous manner. However, the use of animal models still remains a necessity today.

These changes are unfortunately little known by the general public and it is now necessary to stop affirming that the number of animals is going to decrease, no longer oppose *in vitro* and *in vivo* techniques, whereas these techniques are based largely on animals and these technologies are complementary, and no longer delude people into believing that the development of alternative methods can be decreed from above. On the other hand, the prospects offered by these techniques should be studied sector per sector and test by test, while exploiting to a greater extent the data from animal experiments.

What ethics ?

Alongside the reduction of the number of animals used in procedures and the replacement of the use of animals by available alternative methods, 'refinement' is aimed at limiting damage caused to animals. On the regulatory plane, this principle, which meets not only ethical but also scientific goals as the stress that animals undergo can distort results, is embodied in two types of measures: those defining animal accommodation conditions, and those on animal care which are essential.

As regards accommodation, the 1986 directive refers to the recommendations laid down by the Council of Europe which were updated in 2006 and endorsed by the European Commission in 2007. Not all European countries have adapted their facilities. The proposal for a revision, which is aimed in particular

at giving a mandatory nature to these recommendations, raises various problems, especially concerning the timeframes for complying with standards, which weighs directly or indirectly on research budgets.

As regards care, the 1986 directive comprises a series of measures aimed at limiting the damage caused to animals: use of the least sensitive animals, choice of the least painful procedures, regular monitoring, systematic use of anaesthesia or analgesics, euthanasia of animals when limit points are reached, limitation of the possibilities of re-using animals.

Source : APBI - Biosciences Federation

The proposal for a revision has, in this field, introduced new measures deemed positive such as a strengthening of the role veterinarians play, and the introduction of a severity scale. However, the scientific basis of the various measures and their interest regarding animal welfare are questioned.

The European Parliament has adopted several amendments aimed at relaxing the measures proposed by the Commission, and rightly so. Negotiations are continuing however on the conditions for re-using animals, which could compromise some research, and on the definition of 'severity scales' whose application is a prerequisite for that of various other measures, especially regarding re-use.

Apart from the presently discussed measures, special attention must be paid to various essential issues, such as the need for the availability of very high level scientific work on pain suffered by laboratory animals, the training of personnel, or the development of information instruments adapted to various publics. The ongoing discussions are moreover an opportunity to define strategic guidelines for animal research facilities themselves, their geographic distribution and the pooling of equipment such as imaging equipment.

The difficulties encountered result partly from the lack in Europe of reference scientific documents specifying the accommodation and care conditions. Such documents exist in some European countries, but are not harmonised or always validated. This is a major difference with respect to the United States. In a sense, it can be believed that for want of having such a document, the European Commission has been tempted to introduce rules of this type in the directive.

The reactions raised by the proposal to revise the directive have highlighted the need to organise places of open debate. The creation, in some European countries, of national ethics committees on animal experimentation expresses this concern. However, not all European countries have set up such committees. The reactions also underscored a deep communication deficit, for which the scientific community is partly responsible.

Th initial proposal for a revision has indeed been greatly challenged.

The first friction point concerns the extension of the scope of the directive (hitherto limited to vertebrates) to some invertebrates and to some larval and embryonic forms. The European Parliament has corrected most of these measures. However, these questions may be raised again, first because the fields of legislations on animal experimentation are not harmonised in Europe, and, second, because animal protection associations are putting forward in this field a precautionary principle aimed at including in the field of protection animal forms and species that are presumed to feel pain.

The second friction point concerns the criteria taken into account to grant rules offering greater protection to some species. In this field, scientific arguments are interwoven with societal concerns, and both merit being taken into consideration. This however supposes that a consensus is reached and dialogue starts.

The establishment of general bans and of regulatory restrictions remains the most debated principle. The European Parliament has attempted to find a more balanced compromise, and negotiations are continuing on the most controversial points which concern the conditions for using non-human primates, two measures having been introduced by the Commission, one aimed at using only primates born from those raised in captivity (F2 generation), and the other aimed at limiting research and tests on primates to certain debilitating or mortal diseases. However these restrictions also concern the conditions for re-using animals, according to the degree of severity of the procedures carried out.

The ongoing debates demonstrate the difficulty in reconciling a wide variety of concerns related to human health, animal welfare, research freedom and economic constraints.

Referring to the mandatory use of the F2 generation, which is aimed at banning the use of non-human primates captured in nature and which, for some animal protection associations is aimed at eventually avoiding the use of primates in experiments, many questions immediately arose both regarding the pursued aim of improving animal welfare and also the practical feasibility of the envisaged mechanism and the economic repercussions likely to arise. In view of these objections, the European Parliament has planned for a prior impact study to be carried out and has extended the implementation timeframe; the ongoing discussions concern the actual length of this timeframe depending on whether the results of the impact study are awaited or forejudged.

As for the restrictions laid down regarding the use of non-human primates, several objections have been expressed. The effects of such restrictions indeed raise many questions on the appreciation of the research process which cannot be enclosed in a pre-established framework or oriented exclusively by finalised research, on compliance with regulatory provisions making the use of primates mandatory for some tests, and on the delocalisation risk.

Last, referring to the conditions for re-using animals, relaxations are advisable so as not to ban some types of research.

Since the 1986 directive, projects have generally been submitted to an ethical review weighing up the advantages of the use of animals and the attendant disadvantages for them. This review takes place on a case per case basis, taking account of the species chosen, the stress imposed and the means implemented to reduce it. The establishment of general bans or of regulatory restrictions constitutes in this respect a major change in approach, which was made in 2003 when the 'cosmetics' directive was adopted. Such an approach is apparently specific to the European Union.

What governance ?

In this field, the 1986 directive has left it to the Member States to opt between various systems: authorisation or notifica-

tion of persons, establishments or projects. On the basis of these measures, the States have adopted highly variable control and authorisation systems and it is difficult to affirm that such or such a model is better than another. The most administered systems are sometimes those most disputed by associations and, apparently, the setting up of such systems by no means forms an assurance of public tranquillity.

Source : NC3Rs

The proposal to revise the 1986 directive has introduced various measures to frame the authorisation procedures for establishments, persons and projects, and strengthen the control mechanism (inspections twice a year, one being unexpected; control by the European Commission of the Member States' control systems). Referring to projects, the proposal for a revision submits them to an authorisation system, after a favourable ethical review and, under certain conditions, it sets forth that retrospective reviews shall be carried out and non-technical summaries drafted.

The European Parliament has eased the control procedures in some respects and only projects classified as 'moderate' or 'severe' are submitted by it to an authorisation regime.

The risk of an extension of the timeframes and of an increased administrative burden should be taken seriously, as it directly influences the responsiveness of research organisms and of companies and also affects their competitiveness. It is therefore also necessary to introduce more flexibility in this field.

While the principle of pluralistic ethics committees should be adopted and while it is necessary to submit projects to an authorisation system devised in a sufficiently flexible manner, taking account, as in Germany, of experiments performed pursuant to a legal obligation, or taking into consideration the 'risk' incurred, with regard to the species used, or the stress imposed on animals, and while a certain transparency should be ensured within animal experimentation management systems, it is also necessary to ensure that the defined procedures do not excessively or pointlessly hinder research activities.

Also other issues not taken into account in the proposal for a directive should be closely examined by the public authorities, especially the use of opinion polls and the protection that should be afforded to personnel against the unacceptable acts of highly minoritarian extremist groups.

Recommendations

- Reach a balanced revision of the 1986 directive with progressive application of the new measures, especially regarding the conditions for using non-human primates and accommodation and care rules. Flexibility of the administrative and ethical systems is also necessary at European level;

- Combine this revision with a taking into account, in the research and innovation policies, of the need to perfect animal experimentation methods and animal models, and develop alternative methods. Animal research facilities should also now find their place in the European research equipment and innovation strategies;

- Support research at the European and the national level, by setting up pluridisciplinary and partnership teams in order to improve knowledge on laboratory animals, especially regarding the assessment of pain, devise new predictive tools to reduce the number of animals used and replace their use, and support research avoiding the use of animals;

- Improve the operation of the European Centre for the Validation of Alternative Methods (ECVAM), in order to speed up and intensify the validation procedures for alternative techniques;

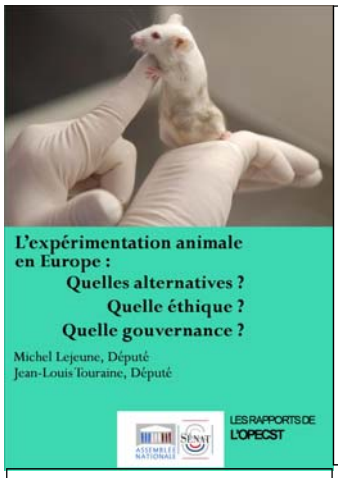
- Create a prestigious Prize to award the results of collaborative work on alternative methods to animal experimentation;

- Promote the exchange of results and encourage laboratories to set up secure data-sharing systems;

- Strengthen the training measures by: setting up a pan-European system of equivalences; completing the training modules; raising the awareness of students; enhancing the role of veterinarians; drafting a guide to the care and use of laboratory animals that can be accessed on the Internet; creating professorial chairs in animal experimentation and alternative methods; and enriching school programmes;

- Promote a better coordination and a better involvement of public authorities by: improving statistical tools; ensuring legal monitoring; defining new strategies on use in *in* vivo sciences, the pooling of animal research facilities and their equipment, and the validation of alternative methods; organising information campaigns; and ensuring the protection of researchers and personnel at establishments breeding and using animals;

- Encourage the scientific community to participate in information and communication campaigns on the conditions for using animals for scientific and experimental purposes, the utility of animal experimentation, and the prospects offered by the development of alternative methods.



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